REMARKS

Claims 49-52, 54-65, and 68-70 are pending in the application. Claims 1-48, 53, 66, and 67 have been cancelled without prejudice or disclaimer. Claims 49, 69 and 70 are amended. Following entry of the amendment, claims 49-52, 54-65, and 68-70 are pending in the application.

Amendment of the claims herein is not to be construed as acquiescence to any rejection made in the instant Office Action or in any previous Office Action, and was done solely to expedite prosecution of the application. Support for the amendment to claims 49, 69 and 70 may at least be found in the originally filed specification at page 58, lines 13-16. No new matter is added. Applicants reserve the right to pursue the claims as originally filed, or substantially similar claims in one or more subsequent patent applications.

Rejections under 35 U.S.C. § 103(a)

The Office rejects claims 49-52, 54-56, 58-65, and 68-69, which are directed to methods for inducing new blood vessel growth in myocardial tissue and improving cardiac function, under 35 U.S.C. § 103(a) as allegedly obvious over one or more of the following references: Isner et al., International Publication No. WO 97/14307 ("Isner"), in view of Hammond et al., U.S. Patent No. 5,880,090, ("Hammond"), and Dillman et al., U.S. Patent No. 6,605,274 ("Dillman"). For the reasons detailed herein, Applicants respectfully disagree with the rejection and request that it be withdrawn.

I. Isner does not teach administration of an effective amount of an angiogenic factor (e.g., GM-CSF, G-CSF, SCF, or an effective fragment thereof).

Applicants' claims recite administering an effective amount of at least one angiogenic factor or an effective fragment thereof to induce blood vessel growth in myocardial tissue and to increase the frequency of endothelial progenitor cells (EPCs). Applicants' specification describes methods for modulating EPC kinetics by administering cytokines (Example 1, page 29-30). Applicants report that their results indicate that "GM-CSF exerts a potent stimulatory effect on EPC kinetics and that such cytokine-induced EPC mobilization can enhance neovascularization of severely ischemic tissues as well as de novo vascularization of previously

avascular sites (page 36, lines 24-28). These results, which represent a significant advance over the prior art, are not described by Isner.

Specifically, the Office states in the Office Action mailed December 16, 2008, page 5, first full paragraph states

> Isner does not teach specifically a further administration of an effective amount of at least one angiogenic factor, specifically a stem cell factor (SCF), a colony stimulating factor (CSF), or an effective fragment thereof into the mammal to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells. (Office action mailed December 16, 2008, page 5, first full paragraph; emphasis present in the original.)

Thus, the Office has indicated that the claimed invention differs from that of Isner because Isner fails to teach the administration of an effective amount of stem cell factor, colony stimulating factor to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells as presently claimed.

II. Isner does not teach systemic administration of an angiogenic factor (e.g., GM-CSF, SCF, or an effective fragment thereof).

The methods of the invention as currently claimed involve the systemic administration of an angiogenic factor. Without in any way acquiescing to the rejection and to claim the invention more completely and accurately, Applicants have amended claims 49, 69, and 70 to recite that the angiogenic factor (e.g., GM-CSF, SCF, or an effective fragment thereof) is administered **systemically**. Claims 51, 52, 54-65, and 68, which depend from claim 49, also contain the features of claim 49, as currently amended.

Isner does not teach the systemic administration of an angiogenic factor, but instead teaches "a method for treating ***ischemic tissue*** in a mammal which comprises ***injecting said tissue*** with an effective amount of a nucleic acid capable of expressing an angiogenic protein" (See Abstract; emphasis added). The tissue injection also applies to combinations with other genes or their encoded gene products, as Isner does not teach the **systemic** administration of an angiogenic factor. That is, the underlying rationale for direct injection of tissue was to overcome the limitation of treatment methods in the prior art which required the repeated doses of angiogenic proteins by intramuscular administration over a range of 10 to 14 days. This limitation is described in the specification at page 1, lines 19-21:

> Thus, one major limitation of recombinant protein therapy is its potential requirement to maintain an optimally ***high and local concentration*** over time. [emphasis added]

In view of this statement, systemic administration of agents presumably was insufficient to provide the ***high and local concentration*** of angiogenic agents over time that was required for the treatment of ischemia. In this regard, Applicants submit that Isner implicitly teaches away from systemic administration of angiogenic agents. Therefore the invention being claimed is distinguishable over Isner because it involves the systemic administration of an angiogenic factor.

III. Isner does not teach methods for monitoring cardiac function.

Applicants' claims, as currently amended, recite monitoring a cardiac function by echocardiography, ventricular end-diastolic dimension (LVEDD), end-systolic dimension (LVESD), change in fractional shortening (FS), wall motion score index (WMSI), electromechanical mapping, cardiac angiography or LV systolic pressure (LVSP). Applicants' specification describes the use of VEGF-2 in a mouse model of myocardial ischemia, and the use of G-CSF and VEGF-2 in a swine model of myocardial ischemia, which resulted in a marked increase in cardiac function (Example 11, pages 47-48) and was associated with the recruitment of bone marrow cells to ischemic cardiac tissues (page 57, lines 16-21). In contrast, Isner does not teach monitoring cardiac function by the diagnostic tests recited in the claims.

The Office also indicates that Isner fails to teach methods for monitoring cardiac function. Specifically, the Office Action of December 16, 2008, states at page 6, first paragraph;): "Isner also does not teach specifically to monitor a cardiac function by one of the recited approaches." (emphasis present in the original). Therefore, Isner does not describe improving cardiac function, as recited in the claims by inducing new blood vessel growth in myocardial tissue. Thus, Applicant's discovery provides a significant advance over the prior art.

IV. There is no motivation to combine Isner and Hammond, which teaches endothelialization of synthetic vascular grafts.

The Office has cited Hammond as allegedly remedying the deficiency of administering an effective amount of at least one angiogenic factor or an effective fragment thereof to induce

blood vessel growth in myocardial tissue and to increase the frequency of endothelial progenitor cells (EPCs) because Hammond discloses the use of stem cell factor and granulocyte macrophage colony stimulating factor for the mobilization of endothelial cell progenitors. Contrary to the Office's assertion, there is no motivation to combine Hammond with Isner as is proper to establish a *prima facie* case of obviousness, see *In re Fine*, 837 F.2d 1071,1075, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

In support of the rejection, the Office alleges that the passage at column 3, lines 28-37 of Hammond discloses that $CD34^+$ circulating cells in the blood can participate in the repair of ischemic tissue. Applicants respectfully disagree. Hammond describes "methods for enhancing the endothelialization of ***synthetic vascular grafts***" (Abstract of the specification; emphasis added). At column 3, lines 28-37, Hammond states:

> It has been demonstrated that $CD34^+$ or $Flk\text{-}1^+$ cell populations (Flk-1 is an endothelial cell marker) derived from peripheral blood include a subset of cells that are capable in culture of differentiating into endothelial-like cells (e.g., Asahara et al., 1997). Asahara et al. ***proposed*** that these circulating $CD34^+$ or $Flk\text{-}1^+$ cells participate in the repair of ischemic tissue. It is disclosed herein that agents capable of increasing the level of blood-borne $CD34^+$ cells can enhance the endothelialization of synthetic vascular grafts. [emphasis added]

When read in the proper context, the citation of Asahara et al., 1997 (Science. 1997 Feb 14;275(5302):964-7) in Hammond does not amount to a specific teaching but a mere ***proposal*** concerning a possible role for $CD34^+$ cells. The results in Asahara et al., 1997, were merely suggestive of a role for $CD34^+$ cells in repair of ischemic tissue based on the "isolation of putative progenitor cells for angiogenesis" (Title). Any connection Hammond attempts to draw between Asahara et al., 1997, and their own data, at best, only suggests a role for EPCs in the endothelialization of synthetic vascular grafts. Importantly, except for mentioning this *proposal*, there is nothing in Hammond that supports a role for EPCs in repairing ischemic tissue. Hammond merely teaches that "agents capable of increasing the level of blood-borne $CD34^+$ cells can enhance the endothelialization of synthetic vascular grafts," which is the only role for EPCs that is addressed by the experiments of Hammond.

The endothelialization of synthetic vascular grafts is unrelated to Applicants claims, which are directed to methods for inducing new blood vessel growth in myocardial tissue and improving cardiac function. Specifically, the grafts described by Hammond are synthetic

substrates on which EPCs attach and coat the surface. In contrast, these processes do not reconstitute, let alone approximate, the multicomponent EPC interactions required for *de novo* blood vessel growth. Moreover, Hammond fails to teach or suggest Applicants claimed invention which recites that the claimed method improves cardiac function. Because the results of Hammond cannot be extended beyond an observation that EPCs participate in the attachment and coating of synthetic vascular grafts, there is no teaching or suggestion to support the combination of Isner with Hammond, which relate to two different processes. Accordingly, when the references cited by the Patent Office fail to establish a *prima facie* case of obviousness, the rejection is improper and must be withdrawn. *In re Fine*, 837 F.2d at 1074, 5 U.S.P.Q.2d at 1598.

V. There is no motivation to combine Isner and Dillman, which describes diagnostic methods for monitoring cardiac function.

To remedy the deficiency of Isner, which fails to teach methods for monitoring cardiac function, the Office cites Dillman as allegedly providing the requisite teaching. The Examiner asserts that it would be obvious for the skilled artisan to monitor the effects of the treatment described by Isner by monitoring cardiac function using the methods described by Dillmann. Applicants respectfully disagree.

The claims are specifically directed to a method of improving cardiac function as measured by echocardiography, ventricular end-diastolic dimension (LVEDD), end-systolic dimension (LVESD), change in fractional shortening (FS), wall motion score index (WMSI), electromechanical mapping, cardiac angiography or LV systolic pressure (LVSP). In contrast, Dillman fails to teach or suggest Applicants' claimed invention, which further recites that the claimed method improves cardiac function. That is, the recitation of these diagnostic methods further define the invention by specifying how to evaluate the improvement of cardiac function. These diagnostic methods are not recited as merely exemplary. Further to this point, Applicants' specification has clearly taught the value of measuring these particular variables as it relates to inducing blood vessel growth and treating cardiac ischemia. In this regard, Applicants have described and enabled the use of these methods for monitoring cardiac function (Examples 8-12, pages 35-58, Figures 8A-C and 11A-11C) Dillmann may describe methods for monitoring the

function of a cardiac tissue, but Dillman says nothing about improving cardiac function using Applicants' method.

In order to establish a *prima facie* case of obviousness, the Federal Circuit requires the Examiner to show some motivation to combine the references that create the case of obviousness. *In re Roufett*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457-1458 (Fed. Cir. 1998). A teaching, suggestion, or motivation to combine cannot be merely derived from the fact that the combination could be made, rather the motivation "must be clear and particular." *In re Dembiczak*, 175 F.3d 994, 50 USPQ 2d 1614 (Fed. Circ. 1999). In *In re Roufett*, the Federal Circuit cautions against inferring the presence of such motivation where it lacks this particularity, especially:

> The Board did not, however, explain what specific understanding or technological principle within the knowledge of one skilled in the art would have suggested the combination. Instead, the Board **merely invoked the high level of skill in the field of art**. If such a rote invocation could suffice to supply a motivation to combine, **the more sophisticated fields would rarely, if ever, experience a patentable technical advance.** Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as **a critical safeguard against hindsight analysis and rote application of the legal test for obviousness**. [emphasis added]

Additionally, MPEP §2142 provides the following guidance regarding reaching a proper determination under 35 U.S.C. §103(a):

> Knowledge of applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based upon applicant"s disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art.

It is not sufficient to show that Applicants' claimed combination *could* be made by rote application of the legal test of obviousness. Other than invoking a high level of skill in the art, the Office has not provided any other motivation to combine Dillman with any of the other cited references to arrive at Applicants' invention. That is, the Examiner must show some particular teaching or suggestion within the references themselves that the combination *should* be made.

Instead, Applicants' own disclosure provides the teaching that these diagnostic methods of monitoring cardiac function are features of the invention. Only from hindsight reasoning does one arrive at Applicants' claim reciting these specific diagnostic methods of monitoring cardiac function. Because the motivation to combine is based either on rote application of the legal test of obviousness or else on hindsight reasonsing, Applicants request reconsideration and withdrawal of the rejections for *prima facie* obviousness relying on Dillman

VI. Applicants' disclosure demonstrates evidence of unexpected and surprisingly effective result.

In their specification, Applicants describe methods of administering an effective amount of a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue and administering to the mammal an effective amotmt of at least one angiogenic factor or an effective fragment thereof to induce new blood vessel growth in myocardial tissue of the mammal and improve cardiac function. Applicants state that this combination is likely to provide a synergistic effect (page 7, line 27) and provide probative, objective evidence that the effect is synergistic, or greater than expected for the methods of monitoring recited in the claims.

Where Applicants are able to show that the claimed invention is unexpectedly superior to the prior art, the unexpected results are sufficient to show that the invention is non-obvious.

> One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of "unexpected results," i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward--that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. *In Re Pravin L. Soni* 54 F.2d 746 at 750; 34 U.S.P.Q.2d 1684 (Fed. Circ. 1995). [emphasis added]

Greater than expected results are evidence of nonobviousness (MPEP §716.02):

> "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). In *Corkhill*, the claimed combination showed an additive result when a diminished result would have been expected. This result was persuasive of nonobviousness even though the result was equal to that of one component alone. **Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism").** *Merck & Co.*

> *Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989). However, a greater than additive effect is not necessarily sufficient to overcome a *prima facie* case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. *Ex parte The NutraSweet Co.*, 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991) (Evidence showing greater than additive sweetness resulting from the claimed mixture of saccharin and L-aspartyl-L-phenylalanine was not sufficient to outweigh the evidence of obviousness because the teachings of the prior art lead to a general expectation of greater than additive sweetening effects when using mixtures of synthetic sweeteners.). [emphasis added]

Thus, evidence of synergism is indicative of non-obviousness (*Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, U.S.P.Q. 2d 1181 (Fed. Cir. 1997).

As evidence that the combination is surprisingly effective, Applicants present data showing the effects of angiogenic gene therapy in combination with cytokine-induced endothelial progenitor cell mobilization in a swine model of chronic myocardial ischemia and a murine model of acute myocardial infarction (pages 54-58). In particular, Applicants direct the Examiner's attention to Examples 8-12, pages 35-58, where Applicants describe *in vivo* experiments in a swine model of acute myocardial infarction (page 46, lines 7-11, and page 46, line 24) and mouse models of acute and chronic. Applicants treated animals with chronic myocardial ischemia (swine) or with acute myocardial infarction with VEGF in combination with cytokines (e.g., G-CSF and/or SCF) and measured the effect of this treatment on cardiac function. Applicants found that "In chronic MI [myocardial ischemia], combo therapy resulted in superior improvement in all indexes of perfusion and function, compared with all other treatment groups." (page 58, lines 4 and 5; emphasis added). Moreover, Applicants disclose that the effect of cytokines in combination with VEGF was synergistic (page 58, lines 18 and 19).

The data used to base these conclusions are shown in Figures 8A-8E and 11A-11C, as measured by echocardiography, ventricular end-diastolic dimension (LVEDD), end-systolic dimension (LVESD), change in fractional shortening (FS), wall motion score index (WMSI), electromechanical mapping, cardiac angiography or LV systolic pressure (LVSP), all of which are recited in the claims. In Figure 11B, the results of combination treatment are clearly synergistic, as the changes in FS (~5%) and RWMS (~ -4) cannot be explained by treatment with either VEGF-2 (FS: ~1%; RWMS: ~ -1) or cytokines (FS: ~ -1%; RWMS: ~ 0.5) alone. That

is, the combined effect cannot be explained merely by taking the sum of the effects of the individual treatments. The same is true of the LVEDP measurements shown in Figure 11C, lower, right panel; the combined reduction in pressure cannot be arrived at simply by the additive effects of the individual treatments. Regarding electromechanical mapping, Figures 8A-8E likewise show that the effect of combination treatment is synergistic and greater than the sum of the individual effects of either VEGF-2 or cytokine treatment alone.

It is the Office's position that the results of the group administered the combination treatment are not surprising or effective. Applicants respectfully disagree. For these assays showing synergistic effects, there is no question that the combination treatment is both surprising and effective, and therefore unexpected. Contrary to the Office's assertion, the degree of enhancement (i.e., synergism) shown is unexpected to an unobvious extent, whether in view of the cited references or when compared side-by-side in Applicants' disclosure. *Arguendo* even if the effects of the individual treatments were multiplied, one would still not have predictably achieved the effect of the combination treatment to the degree Applicant's have disclosed.

Regarding the LVEDD, LVESD, hemodynamic measurements in Figure 11C, the data from the combination treatment also shows the effects are unexpected. That is, the *changes* in the measurements for each of the treatment groups, when normalized to the saline control group, are unexpected to an unobvious extent. Applicants submit that for these measurements it is appropriate to evaluate the change in value relative to the control instead of the absolute value of each measurement. Specifically, addition or multiplication of the absolute value of each of the measurements does not yield any useful comparisons of the data.

In the LVEDD, LVESD, and hemodynamic (+ dP/dt and – dP/dt) measurements in Figure 11C, the effect of cytokines is statistically indistinguishable from the control. When the LVEDD and LVESD measurements for cytokines are normalized to control, it can be shown the effect they have is effectively near zero. This is contrary the Office's assertion on page 17 that angiogenic effects of the cytokines predictably contribute to improving cardiac function. Based on the probative evidence, one would not predict any contribution to cardiac function from the administration of cytokines alone, regardless of any angiogenic effect of the cytokines. The effects of administering the nucleic acid encoding an angiogenic protein would not be predictably complemented or enhanced by additionally administering cytokines, and one cannot

arrive at such a conclusion, unless one had measured the actual effect of the combination, as Applicants have done.

Regarding the changes in echocardiography shown in Figure 11A, the individual changes in the groups administered VEGF-2 alone (30% - 25% = 5%) or cytokines alone (27% - 25% = 2%) also do not explain the extent of change observed in the group administered the combination (39% - 25% = 14%), when all test values are normalized to the control. Based on the individual VEGF-2 (5%) and cytokine (2%) treatments, one would, at best, expect their combination to yield a 7% change (additive) or at most 10% change (multiplicative). However, the actual value of 14% is far greater than either of these values.

When the changes from administration of cytokines are quantified together with the changes from adminstration of VEGF-2, this does not result in the extent of change seen in the combination treatment in LVEDD, LVESD, hemodynamic tests, and echocardiography. Therefore one would not expect any of these results to an obvious extent, in view of Applicants' own data regarding the separate administration of the components of the combination, let alone from the references cited by the Office.

Thus, Applicants have provided evidence showing that the results obtained with the claimed invention are superior to what was expected based on the prior art to an unobvious extent. In particular, the combination of administering a nucleic acid encoding VEGF-2 and G-CSF and/or SCF, which are recited in Claims 69 and 70, was shown by the Applicants to demonstrate these unexpected and surprising effects. None of the prior art references cited by the Examiner teach or suggest that using combination therapy for the treatment of myocardial ischemia would be so surprisingly effective. This is especially true, given that none of the references teach that VEGF when administered with a cytokine would have a synergistic effect on cardiac function in ischemic myocardial tissues. Accordingly, the obviousness rejection of the claims should be withdrawn.

VII. Asahara does not teach the <u>combination</u> of a nucleic acid encoding at least one angiogenic protein and at least one angiogenic factor

The Examiner further rejects claims 50, 51, and 57 under 35 U.S.C. § 103(a) over Isner, Hammond, Dillman and Asahara et al., (EMBO J. 18:3964-3972, 1999; "Asahara"). Asahara describes the use of VEGF to induce the mobilization of bone marrow-derived EPCs, and notes

that these EPCs can contribute to corneal neovascularization. Importantly, Asahara failed to appreciate, as Applicants did, that the **combination** of a nucleic acid encoding at least one angiogenic protein and at least one angiogenic factor, enhances the induction of blood vessel growth in a myocardial tissue. Applicants' unexpected and surprisingly effective results described in Section VI support the fact that even applying the teaching Asahara would not have resulted in possession of the invention being claimed. Thus, Asahara also fails to teach or suggest Applicants' claimed invention, and the rejection of the claims over Isner, Hammond, Dillman and Asahara should also be withdrawn.

VIII. There is no motivation to combine Isner, Hammond, Dillman, which describes diagnostic methods for monitoring cardiac function.

The Office further rejects claim 70 over Isner, in view of Hammond, Dillman, and further in view of Coleman (U.S. 7,273,751; "Coleman") or Hu et al. (U.S. 6,734,285; "Hu"). The Office acknowledges that Isner, Hammond and Dillman fail to describe the use of VEGF-2 to new blood vessel growth in myocardial tissue and improve cardiac function. To remedy the deficiencies of Isner, Hammond, and Dillman the Office cites Coleman and Hu. The Examiner indicates that Coleman and Hu describe the use of VEGF-2 as an angiogenic factor. Specifically, at page 11, beginning at the second full paragraph, the Office Action of December 16, 2008, states:

> Accordingly, it would have been obvious for an ordinary skilled artisan to further modify the method of Isner, Hammond et al and Dillman et al. by also administering to the treated mammal an effective amount of a nucleic acid encoding VEGF-2 in to the myocardial tissue in light of the teachings of either Coleman or Hu.
>
> An ordinary skilled artisan would have been motivated to carry out the above modifications because both Coleman and Hu et al already taught separately that VEGF-2 is a potent angiogenic factor . . .

The Examiner relies on Hu and Coleman to provide the motivation to use VEGF-2 in combination with a nucleic acid encoding at least one angiogenic protein to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells. However, Hu and Coleman fail to provide the necessary motivation to use VEGF-2 in combination with a nucleic acid encoding an angiogenic protein, as do Isner, Hammond, and/or Dillman. Instead, Hu and

Coleman both teach that VEGF-2 is efficacious on its own, and neither of these references teaches that it is necessary or desirable to administer VEGF-2 in combination with another factor. However, even if Hu or Coleman could be combined *arguendo* with Isner, Hammond, and Dillman, the combination still does not provide any expectation of yielding the unexpected and surprisingly effective results of the combination provided by Applicants' invention (Section VI).

IX. Summary.

In conclusion, Isner does not describe all the features of the invention being claimed (Sections I-III). Furthermore, the cited references do not make up for the deficiences of Isner to put one skilled in the art in possession of Applicants' invention. Specifically, there is no motivation to combine Hammond with Isner (or any of the other references) to arrive at Applicant's invention, and *arguendo* even if there were, Hammond does not teach a relationship between EPCs and new blood vessel growth (v. endothelialization of synthetic grafts) (Section IV). There is also no motivation to combine Dillman with Isner or any of the other references. Dillman only lists possible methods for monitoring cardiac function, but provides no teaching otherwise that would successfully lead one skilled in the art to adopt these approaches. Rather the motivation is found in Applicants' specification which describes the effectiveness of these methods in Examples 8-12, pages 35-58 of the specification as filed (Section V). For these reasons, any combination of Isner, Hammond, and Dillman does not make out a *prima facie* case of obviousness and this rejection should be withdrawn.

Applicants were the first to appreciate that blood vessel growth could be induced using such methods, and that the growth of such blood vessels would improve cardiac function. Importantly, Applicants have shown unexpected results that support the patentability of the invention being claimed (Section VI). Applicants' disclosure demonstrates results that cannot be merely explained by additive effects, and which one would expect only with the benefit of hindsight. The results show unexpected effects greater than simple additive effects or else they show synergistic effects. For these reasons, Applicants' invention is patentable over the previous references (i.e., Isner, Hammond, and Dillman) or in further view of any one or more of Asahara, Hu, and Coleman. Asahara simply does not teach the combination of administering a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the

myocardial tissue **and** systemically administering at least one angiogenic factor or an effective fragment thereof. There is also no motivation to combine Hu or Coleman with any of the other cited references because neither of these references teaches that it is necessary or desirable to administer VEGF-2 in combination with another factor. Nevertheless, one still would not have expected the surprisingly effective results of the combination therapy based on any combination of the cited references. Thus, there is no expectation of success to arrive at Applicants' claimed invention based on Isner, in view of Hammond and Dillman, and in further view of Asahara, Hu, or Coleman.

None of the references cited by the Office, alone or in any combination, teaches or suggests Applicants' claimed invention, especially in view of the surprising and unexpected results which the invention achieves. Furthermore, it is not sufficient that one **could** have made the combination of the references, the cited references must suggest the desirability of making the claimed combination and must further indicate that **the combination if made would have succeeded**. Therefore, the references cited by the Examiner, considered as a whole and within relation to each other, do not make out a *prima facie* case of obviousness to support a rejection under 35 U.S.C. 103(a). Accordingly, Applicants request reconsideration and withdrawal of all rejections under 35 U.S.C. 103(a) based on these cited references.

Double Patenting

Applicants acknowledge that claims 49-52, 54-65, and 68-69 are provisionally rejected over copending U.S. application No. 10/714,574 in view of Dillman alone or in view of Dillman and Asahara. With regard to the provisional double patenting rejection over copending application No. 10/714,574, Applicants submit that upon consideration and entry of the instant Amendment and Response, the provisional double-patenting rejection will be the only rejection remaining in the instant application. Therefore, pursuant to M.P.E.P. § 822.01, Applicants respectfully request that the provisional obviousness-type double patent application be withdrawn so that the instant application may proceed to allowance.

CONCLUSION

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of all rejections and allowance of the application with claims 49-52, 54-65, and 68-70 presented herein. In advance of the issuance of a final Office Action, Applicants invite the Examiner to call the undersigned at the telephone number indicated below to schedule an interview.

Applicants believe that no fee is due to consider the present amendment. Nevertheless, the Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105.

Dated: March 16, 2009

Respectfully submitted,

By _____

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